National Academy of Clinical Biochemistry Guidelines for the Use of Tumor Markers in Cervical Cancer

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Abbreviations: CEA, carcinoembryonic antigen; CT, computerized tomography; EORTC, European Organisation for the Research and Treatment of Cancer; FIGO, International Federation of Obstetrics and Gynecology; HPV, human papilloma virus; LOE, levels of evidence; MRI, magnetic resonance imaging; SCC, squamous cell carcinoma antigen; TPA, tissue polypeptide antigen; TPS, tissue polypeptide specific antigen.

INTRODUCTION

Cancer of the uterine cervix is the major cause of death from gynecologic cancer worldwide. Reported incidence rates in developing countries are much higher than those in developed countries, ranging from 83.2 per 100,000 women in Recife, Brazil, to 3 per 100,000 for non-Jews in Israel (1,2). In 2004, an estimated 10,520 women were diagnosed with cervical cancer in the United States with 3,900 estimated deaths (3). The mean age for cervical cancer is 51 years (1). Cervical cancer progresses slowly from pre-invasive cervical intraepithelial neoplasia (CIN) to invasive cancer. Screening asymptomatic women with regular Papanicolau (PAP) smears allows diagnosis of treatable pre-invasive lesions (4). However, in developed countries, most cases of cervical cancer occur in women who have not had regular PAP smear screening. As screening facilities are not readily available in developing countries, in these countries most women present with advanced stage disease that may have already spread into the bladder, rectum, pelvic nerves, or bone (1).

Abnormal vaginal bleeding is the most common symptom. This includes post-coital, inter-menstrual, or postmenopausal bleeding. However, early stage cervical cancer is often asymptomatic until quite advanced in women who are not sexually active (1). Large tumors may present with vaginal discharge. In advanced cases, pelvic pain, pressure symptoms pertaining to the bowel or bladder, and occasionally vaginal loss of urine or faeces may be present (1).

The PAP smear test is used to screen asymptomatic women for cervical cancer and has been shown to reduce both the incidence and mortality of this malignancy in Western countries (4). Pre-malignant CIN lesions can be detected and treated by loop electrosurgical excision, cryosurgery, CO_2 laser, or hysterectomy (4). It is generally accepted that specific high-risk human papilloma virus (HPV) types are causally involved in the pathogenesis of cervical cancer. The high-risk HPV types 16, 18, 45, and 56 are predominantly found in high-grade intraepithelial lesions and cervical cancers (5,6). It has been suggested that HPV testing can improve the efficacy of cervical cancer screening (4).

Approximately 85% of cervical cancers are of the squamous cell type. Other histological types most frequently found are adenocarcinoma (circa 10-15%) and adenosquamous carcinoma (circa 3%). Treatment planning of patients with cervical cancer is primarily determined by the clinical stage of disease, usually according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria (1). Early stage cervical cancer (Stage IB1, IIA, tumor < 4 cm diameter) is primarily treated with radical hysterectomy and pelvic lymphadenectomy (1). In case of pelvic lymph node metastases, parametrial involvement, or positive surgical margins, adjuvant radiation therapy to the pelvis is given. In these cases, it has been reported that concomitant chemoradiation with platinum-based chemotherapy significantly improved disease-free survival and survival, compared to

radiotherapy only (7). Bulky stage IB2 or IIA cancer can be treated either by radical surgery, concomitant chemoradiation, or neoadjuvant chemotherapy followed by radical surgery (1,8-10). For locally advanced cervical cancer (stage IIB, III, IVA) concomitant chemoradiation, with weekly single agent cisplatin, has been the standard since 2000 (8,9). Neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical cancer has shown disappointing results in terms of survival. However, a recent meta-analysis suggested that both dose intensity of cisplatin and interval duration between the chemotherapy cycles might be of critical importance and suggested it needed further study (10). A comparison of neoadjuvant chemotherapy followed by surgery vs chemoradiation is presently ongoing within the European Organisation for the Research and Treatment of Cancer (EORTC) Gynecologic Cancer Group (Protocol 55994), in patients with Stage IB2, Stage IIA > 4 cm, or Stage IIB cervical cancer. The role of chemotherapy in patients with recurrent or metastatic disease is merely palliative.

Patients with Stage IB or IIA disease (early stage disease) have an overall 5-year survival between 66 and 95% (1). Patients with more advanced stage disease (Stage IIB and higher) have a 5-year survival between 9 and 64% (1). The FIGO staging procedure fails to detect lymph node metastases in approximately 15-20% of patients with early stage cervical cancer (1). However, the presence of lymph node metastases is the most important prognostic factor associated with recurrent disease and poor survival (1,11-13). The five-year survival rate of patients with Stage IB or IIA cervical cancer declines dramatically from approximately 80-95% in patients without lymph node metastases to approximately 50-65% in patients with positive lymph nodes (1).

Follow-up of patients after primary treatment consists of gynecological investigation. Dependent on clinical symptoms and physical findings, additional cytological or histological investigations, computed tomography (CT) scan, magnetic resonance imaging (MRI), or ultrasound can be performed. The aim of follow-up after initial treatment is to detect recurrent disease in an early phase in order to improve prognosis. It has been suggested that tumor markers may be helpful in the management of patients with cervical cancer, for example in predicting prognosis, in selecting high risk patients who need adjuvant treatment, or in monitoring after primary treatment. The aim of this article is to present guidelines on the possible clinical utility of tumor markers in cervical cancer, especially in squamous cell cervical cancer.

CURRENTLY AVAILABLE MARKERS FOR CERVICAL CANCER

Tumor markers that may be helpful in the management of patients with cervical cancer are listed in Table 1, together with the phase of development for each marker as well as the level of evidence (LOE) for its clinical use. Only tumor markers for which possible clinical usefulness

has been demonstrated in several studies are listed in the table. For squamous cell cervical cancer, squamous cell carcinoma antigen (SCC) is the marker of choice. Serum levels of SCC have been found to correlate with tumor stage, tumor size, residual tumor after treatment, recurrent or progressive disease, and survival in patients with squamous cell cervical cancer (14-41). Carcinoembryonic antigen (CEA) and CA125 in particular have demonstrated possible utility in patients with cervical adenocarcinoma (42-46). These guidelines focus on the use of SCC in squamous cell cervical cancer, because squamous cell cervical cancer is the most prevalent histologic type of cervical cancer and SCC seems the most promising marker.

TUMOR MARKERS IN CERVICAL CANCER: NACB RECOMMENDATIONS

Table 2 summarises the National Academy of Clinical Biochemistry (NACB) guidelines for the use of SCC in squamous cell cervical cancer together with recommendations from other representative guidelines published on the use of tumor markers in cervical cancer. While other markers have been investigated (Table 1), based on currently available evidence only the use of SCC can be recommended in squamous cell cervical cancer. Below we present a more detailed discussion of its use.

Squamous cell carcinoma antigen (SCC)

Biochemistry of SCC.

Squamous cell carcinoma antigen (SCC) is a sub-fraction of TA-4, a tumor-associated antigen first described by Kato et al. in 1977 (47). SCC belongs to the family of serine protease inhibitors (48). In most studies, it is total SCC that is measured and used to determine clinical utility.

Molecular cloning of the SCC genomic region has revealed the presence of two genes, SCC1 and SCC2, which are both located on chromosome 18q21.3 and arrayed in tandem. SCC1 codes for the neutral isoform of SCC and SCC2 codes for the acidic isoform (49). The neutral isoform is detected in both normal epithelial cells and malignant tissues, whereas the acidic isoform is found in tumor cells, especially those located at the periphery of the tumor, and in the sera of cancer patients with well-differentiated squamous cell carcinomas (50). It has been suggested that SCC1 and SCC2 are capable of regulating proteolytic events involved in both normal (e.g. tissue remodeling, protein processing) and pathologic processes (e.g. tumor progression) (51). SCC1 and SCC2 are almost identical, differing only in their reactive site loops. There is evidence that SCC1 and SCC2 have different biological functions (49,51,52).

Reference intervals for SCC.

In apparently healthy women, the 99th percentile of circulating SCC is found at a level of 1.9 μg/L. Most studies have adopted a cut-off point between 2.0 and 2.5 μg/L. SCC is not organ-specific (for cervix) or malignancy-specific. Elevated levels have been found in patients with squamous cell carcinomas of the vulva, vagina, head and neck, esophagus, and lung (19,53,54), as well as in patients with benign diseases of the skin (e.g. psoriasis, eczema), lung (e.g. sarcoidosis), liver and kidney. Very high values (up to 18 μg/L) have been found in patients with renal failure, lung disease, head and neck tumors (53). There is no cut-off point that is specific for cervical malignancy.

Clinical utility of SCC in squamous cell cervical cancer

Screening and diagnosis. SCC is not sufficiently sensitive (particularly in early stage disease) or specific for cervical cancer for use in screening. Diagnosis in all cases is based on histopathological findings. Elevated levels of serum SCC are found at initial diagnosis in approximately 60% of patients with cervical cancer, when all stages are included (55). More specifically, serum SCC is elevated in approximately 24-53 % of patients with Stage IB or IIA squamous cell cervical cancer, and in approximately 75-90% of patients with advanced stage (FIGO IIB and higher) disease (19,22-24,28,38). Serum SSC levels correlate significantly with tumor stage (17,20,21,24,27,38,41).

A number of studies have examined the utility of elevated pre-treatment SCC as a marker for the presence of lymph node metastases (14,20,22,24,28,37,39,56-60). In patients with Stage IB or IIA squamous cell cervical cancer, sensitivity of an elevated pre-treatment level of SCC to detect lymph node metastases has ranged from 60 to 87% with specificity ranging from 41 to 91% (14,20,22,24,37,60). In a large series of such patients elevated pretreatment SCC, large tumor size, and lymphovascular space involvement were independent risk factors for the presence of lymph node metastases (22). In another study, after controlling for stage, only SCC levels higher than 10 μg/L were associated with enlarged lymph nodes shown on CT scan in patients with squamous cell cervical cancer treated by radiotherapy (28). Massuger et al. (59) combined SCC (cut-off value 2.5 μg/L) with CA125 in women with stage IB/IIA cervical cancer that included all histological types and reported a positive predictive value of 76% in detecting lymph node metastases or lymphovascular space involvement.

Several authors have suggested using higher cutoff values for SCC to identify patients with squamous cell cervical carcinoma that has spread to lymph nodes. Takeshima *et al*. reported a sensitivity of 59% and specificity of 94% using a cutoff value of 4 μg/L (39). Bolger *et al*. reported sensitivities for lymph node metastases of 58%, 45%, and 23% using cutoffs

of 2, 4, and 8.6 μg/L respectively (57). The corresponding positive predictive values were 51%, 70%, and 100%. Negative predictive values varied between 84 and 89% (57). Lin *et al*. reported that about 86% of the patients in a large series with squamous cell cervical carcinoma with SCC levels below 8 μg/L showed no lymph node metastases, while about 65% of the patients with serum levels above 8 μg/L exhibited nodal metastases (58).

Gaarenstroom *et al* (24) have reported that the clinical performance of SCC over a range of decision levels is poor in identifying lymph node metastases, as reflected by the diagonal appearance of the receiver operating characteristic curve. They concluded that a normal initial SCC level cannot exclude the presence of lymph node metastases and extra-cervical spread, and hence is of limited use in treatment planning. However a high pre-treatment serum SCC level (>8 μg/L) dramatically increases the likelihood of lymph node metastases or extra-cervical spread (28,57,58). Clinical trials should be conducted to determine whether chemoradiation is more effective than surgery as the primary mode of treatment for patients with low stage (IB or IIA) cervical cancer and high pre-treatment SCC levels.

Prognosis. An elevated pre-treatment SCC level has been found to be an independent risk factor of poor survival in several studies (14,22,28,37). Duk *et al* reported that the pre-treatment SCC level was the only independent risk factor of poor survival in 260 patients with Stage IB or IIA disease (22). However, in contrast with other reports, lymph node status showed no independent prognostic value in their study (22). Åvall-Lundqvist *et al* (14) found that SCC and CA125, in addition to stage, were significantly related to survival in the multivariate analysis of 142 patients with cervical cancer ranging from Stage IA through IVB (14). Scambia *et al* concluded from their multivariate analysis of 102 women with locally advanced squamous cell cancer or adenocarcinoma of the cervix that a SCC level greater than 5 μg/L was an independent predictor of response to neoadjuvant chemotherapy and poor survival (37). Finally, Hong *et al* found that a pre-treatment SCC level greater than 10 μg/L [but not between 2 and 10 μg/L], had a significant impact on survival in the multivariate analysis in 401 patients with Stage I to IVA squamous cell cervical cancer primarily treated with radiotherapy (28).

It has been suggested that the pre-treatment level of SCC can identify patients who require intensive or additional treatment and hence may be of value in treatment planning in the individual patient (22,28,59). Chou *et al* also found that pre-treatment SCC level, along with tumor size, was useful in predicting recurrence and the need for postoperative adjuvant therapy (18). However, formal trials are required to substantiate these claims and to establish

that aggressive treatment triggered by elevated pre-treatment SCC levels actually improves pelvic control and survival.

Use of SCC in monitoring response to treatment and early detection of recurrence. Several studies have concluded that serum SCC is useful in monitoring the course of squamous cell cervical cancer following primary therapy (15-17,20,21,26,27,32,34,36-38,41,54). Persistently elevated and/or increasing serum SCC levels after treatment suggest tumor persistence or progressive disease (16,27,28,37,41,54). Hong et al. found that patients with residual induration and/or persistently elevated SCC level at 2-3 months after radiotherapy had a significantly higher incidence of treatment failure (28). They suggested that a combination of clinical pelvic examination and SCC levels provides useful information for the need of further work-up and management (28). Scambia *et al* reported that a pre-treatment SCC level greater than 5 μg/L was an independent predictor of response to neoadjuvant chemotherapy (37). Patients who were unresponsive to chemotherapy had significant higher SCC values than those who showed complete or partial response (37). Scambia also found a correlation between post-treatment SCC levels with response to chemotherapy. None of the patients with a complete response had serum SCC levels greater than 5 μg/L, while 82% of the unresponsive patients had abnormal marker values (37). The overall correlation between the clinical course of the disease and the variation of SCC levels was 83% (37). The authors suggested that SCC might provide useful information to improve the prognostic characterization and disease monitoring of patients with locally advanced cervical cancer undergoing neoadjuvant chemotherapy (37). Bae *et al* also reported that an elevated pre-treatment SCC and/or CEA level can be used to predict the clinical response to neoadjuvant chemotherapy in a series of 67 patients with squamous cell cervical cancer Stage IB2, IIA, or IIB (56).

Serum SCC level has a sensitivity between 56 and 86% and specificity between 83 and 100% for detecting recurrent squamous cell cervical cancer (15,17,21,25,27,30,36,38,41). Using SCC, a lead-time of up to 14 months for detecting recurrent disease has been reported, with a mean or median between 2 and 6 months (15,17,25-27,29,30,32,34,36). Although SCC is suitable for monitoring the course of disease and shows a strong correlation with the clinical course, it is not yet known whether earlier detection of recurrent disease influences treatment outcome and prognosis. At most 10% of patients with recurrent disease can be cured. Furthermore, most patients (80%) with recurrent disease have clinical symptoms.

CONCLUSIONS

The NACB recommendations for the use of tumor markers are presented in Table 2, but in brief, although SCC is not suitable for screening or diagnosis of cervical cancer, serum SCC levels correlate with tumor stage, tumor size, residual tumor after treatment, recurrent or progressive disease, and survival. Highly elevated pre-treatment SCC levels may indicate the presence of lymph node metastases or extra-cervical spread, but a normal SCC level does not exclude the presence of lymph node metastases.

Pre-treatment SCC levels may be used to individualize treatment planning, in particular in patients with low stage squamous cell cervical cancer, but no randomised trials have yet been conducted to confirm this hypothesis. An elevated pre-treatment SCC level has been found to be an independent risk factor for poor survival in several studies. Whether pre-treatment SCC level is really useful in clinical practice remains uncertain. There is no evidence that more aggressive treatment improves pelvic control and survival in patients with elevated SCC levels. SCC shows a strong correlation with the clinical course and is suitable for monitoring disease after primary treatment, and may therefore be useful in the management of patients. However, there is as yet no evidence that earlier detection of recurrent disease influences treatment outcome or prognosis after primary treatment.

Table 1. Currently available and potentially useful serum markers for cervical cancer.

Cancer marker	Proposed use	Phase of development	LOE	References
SCC	Pre-treatment identification of high risk group with lymph node metastases in squamous cell cervical cancer	Needs further evaluation for clinical usefulness	III-IV	14,20,22,24,28,37,39, 56-60
	Pre-treatment prediction of prognosis in squamous cell cervical cancer	Independent prognostic value in several studies, not validated for individualizing treatment	III-IV	14,18,22,28,37
	Prediction of response to treatment in squamous cell cervical cancer	Needs further evaluation	III-IV	18,28,33,34,37, 41,56
	Monitoring disease and detecting recurrent disease in squamous cell cervical cancer	Strong correlation with course of disease, in clinical use in some centers	III-IV	15-17,21,25-27,29-32,34-36
CA125	Pre-treatment prediction of prognosis, in particular in cervical adenocarcinoma	Needs further evaluation	III-IV	14,44
	Preoperative prediction of the presence of lymph node metastases, in particular in cervical adenocarcinoma	Needs further evaluation	III-IV	14,44,59
	Monitoring disease, in particular in cervical adenocarcinoma	Needs further evaluation	IV	42,43,45,46
CEA	Pre-treatment prediction of prognosis	Results conflicting, needs further evaluation	III-IV	14,36,42,44,56,65
	Preoperative prediction of the presence of lymph node metastases, in particular in cervical adenocarcinoma	Needs further evaluation	III-IV	14,44,59
	Pre-treatment prediction of clinical response to neoadjuvant chemotherapy	Needs further evaluation	IV	56
Cytokeratins (TPA, TPS, Cyfra21-1)	Pre-treatment prediction of prognosis	Needs further evaluation, results conflicting	III-IV	14,24,35,61,62
	Monitoring disease after primary treatment	Needs further evaluation, results conflicting	III-IV	46,63-68

Table 2. Recommendations for use of tumor markers in squamous cell cervical cancer by the NACB.

Marker	Application	NACB 2005
SCC	Pre-treatment identification of high risk group with lymph node metastases	Possibly useful, needs further study
	For predicting prognosis	Possibly useful, needs further study
	For prediction of response to treatment	Possibly useful, needs further study
	For monitoring disease and detecting recurrent disease	Possibly useful, needs further study

SCC, squamous cell carcinoma antigen; NACB, National Academy of Clinical Biochemistry

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